WEST Search History

DATE: Monday, March 17, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L17	l13 and (Fas or anti-fas) same antibod$ and methotrex$	11	L17
L16	l13 and methotrex$	11	L16
L15	l10 and (Fas or anti-fas) same antibod$	3	L15
L14	L13 and l12	0	L14
L13	L4 and (arthrit$)	38	L13
L12	L10 and @ad<20011120	42	L12
L11	L10 adn @ad<20011120	20449421	L11
L10	(autoimmun$ or arthriti$) same (folate or dihydrofolate adj reductase) with (antagon$ or inhibit$)	47	L10
L9	(autoimmun$ or arthriti$) and (folate or dihydrofolate adj reductase) with (antagon$ or inhibit$)	295	L9
L8	(autoimmun$ or arthriti$) (folate or dihydrofolate adj reductase) with (antagon$ or inhibit$)	61545	L8
L7	L3 and (folate or dihydrofolate adj reductase) with (antagon$ or inhibit$)	0	L7
L6	L3 and (folate or dihydrofolate)	20	L6
L5	L3 and (folate or dihyrofolate)	2	L5
L4	L3 and (Fas or anti-fas) same antibody	60	L4
L3	L1 and @ad<19990524	439	L3
L2	L1 and @ad<20000524	585	L2
L1	(autoimmun$ or auto-immun$) with (treat$ or prevent$ therap$) same apoptosis	1041	L1

END OF SEARCH HISTORY

Generate Collection

L4: Entry 19 of 60 File: USPT Apr 24, 2001

DOCUMENT-IDENTIFIER: US 6221615 B1
TITLE: Peptides and compositions which modulate apoptosis

DATE FILED (1):
19990125

Brief Summary Text (16):
The present invention is further directed to methods for inducing or suppressing apoptosis in the cells and/or tissues of individuals suffering from degenerative disorders characterized by inappropriate cell proliferation or inappropriate cell death, respectively. Degenerative disorders characterized by inappropriate cell proliferation include, for example, inflammatory conditions, cancer, including lymphomas, such as prostate hyperplasia, genotypic tumors, etc. Degenerative disorders characterized by inappropriate cell death include, for example, autoimmune diseases, acquired immunodeficiency disease (AIDS), cell death due to radiation therapy or chemotherapy, neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, etc.

Detailed Description Text (106):
In a specific example, microinjection of bacterially-expressed GST-Bcl-x.sub.L, but not GST alone, efficiently protected HeLa cells from death induced by Fas ligation (using an anti-FAS antibody) in the presence of cycloheximide (FIG. 12). Co-injection of a 15 amino acid Bak GD domain peptide (Bak-15), which disrupts GD domain-mediated interactions with Bcl-x.sub.L (see FIG. 10), greatly attenuated the protective effect of Bcl-x.sub.L in this assay. A mutant Bak GD domain peptide (Bak-15L78A), in which an alanine was substituted for a leucine at position 78, did not block Bcl-x.sub.L -mediated protection from Fas-induced death. The ability of GD domain peptide variants to inhibit the function of Bcl-x.sub.L correlated with their ability to bind to Bcl-x.sub.L (see FIG. 10). Under these conditions, neither peptide had an effect on cell viability in the absence of anti-Fas treatment. Similar results were obtained with MRC5 human diploid fibroblasts where protection from anti-Fas-induced death by microinjected Bcl-x.sub.L was inhibited by co-injection of the wild-type, but not mutant, Bak BH3 peptide.

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L4: Entry 13 of 60 File: USPT Oct 23, 2001

DOCUMENT-IDENTIFIER: US 6306395 B1
TITLE: Fas antigen derivatives

DATE FILED (1):
19981102

Brief Summary Text (5):
It has been remained unexplained for a long time about the true character of Fas antigen which is a monoclonal antibody obtained by immunizing mice with human fibroblasts, originally found by Yonehara, S. et al. (J. Exp. Med., vol. 169, pp. 1747-1756, 1989) as a cell surface antigen which is recognized by an anti-Fas antibody capable of inducing apoptosis in certain cells (Yonehara, S. et al.) and transfers a signal of apoptosis to the cells.

Brief Summary Text (16):
Participation of apoptosis by Fas ligand has been suggested also in viral fulminant hepatitis and the like diseases (Nagata, S. et al., Immunol. Today, vol. 16, pp. 39-43, 1995). Thus, as the relationship between Fas antigen-mediated apoptosis and diseases has been revealed, great concern has been directed toward the application of Fas ligand or Fas antigen to the treatment of diseases which are accompanied by abnormal apoptosis, namely the aforementioned autoimmune diseases, rheumatism, AIDS and the like.

Brief Summary Text (17):
Examples of the substance which inhibits Fas antigen-mediated apoptosis so far reported include a .DELTA. TM type Fas antigen, a fusion protein of the extracellular region of Fas antigen with the Fc region of immunoglobulin G (IgG) and a fragment of anti-Fas antibody (Dhein J. et al., Nature, vol. 373, pp. 438-441, 1995) and an anti-Fas antagonist antibody (Alderson M. A. et al., Int. Immunol., vol. 6, pp. 1799-1806, 1994).

Brief Summary Text (18):
Nagata et al. have also reported that they succeeded in obtaining an antibody against the Fas ligand, and that such antibody was capable of suppressing the apoptosis (Masato Tanaka, et al., EMBO Journal, vol. 14, pp. 1129-1135, 1995; International Patent Application Laid-Open No. WO95/13293).

Detailed Description Text (33):
1) cysteine is introduced into the C-terminus and then cross-linking is effected using two types of activation linkers. There is a method for the introduction of cysteine in which cysteine amide or carboxypeptidase Y is used. When the C-terminus is lysine, lysine endopeptidase is used. Also, when free cysteine is present, protection is carried out in advance by alkylation prior to the introduction of cysteine into the C-terminus. Thereafter, cross-linking is carried out using activation linkers. For example, N,N'-o-phenylene dimaleimide (Glennie, M.J. et al., J. Immunol., vol. 139, pp. 2367-2375, 1987) or the like as a divalent cross-linking agent and a tris-maleimide compound (Japanese Patent Application Kokai No. 6-228091) or the like as a trivalent cross-linking agent have been used in the cross-linking of antibodies and can be applied to the novel Fas antigen derivative of the present invention to form a dimer and a trimer, respectively.

Detailed Description Text (53):
Since the novel Fas antigen derivative of the present invention can control Fas antigen-mediated apoptosis, it is useful for the prevention and treatment of diseases related to the sthenia or failure of Fas antigen-mediated apoptosis induced in the living body. For example, since a preferred novel Fas antigen derivative of

the present invention can inhibit induction of apoptosis by competitively inhibiting bonding between Fas ligand and Fas antigen, it is possible to prevent reduction of functions of tissues and organs by inhibiting apoptosis of hepatic cells and the like in the case of hepatitis and the like serious infectious diseases and thereby preventing rapid reduction of cells in major organs and tissues, and it can be used for the treatment of infectious diseases caused by viruses and the like and complications thereof, for example as a drug for use in the treatment of influenza, AIDS, hepatitis and the like diseases. It is also useful for the treatment of certain autoimmune diseases such as diabetes, myocardiopathy in reperfusion injury and the like ischemic heart diseases, nephritis, multiple organ failure and organ preservation and graft versus host disease (GVHD) at the time of organ transplantation.

Detailed Description Text (54):
Since the novel Fas antigen derivative of the present invention binds to Fas ligand with more specific and high affinity, it can be used for the detection of Fas ligand. Also, since it keeps at least a part of the antigenicity of Fas antigen, it can bind to anti-Fas antibody and therefore is effective in inhibiting apoptosis caused by the anti-Fas antibody.

Detailed Description Text (67):
In addition, the DNA fragment of the second aspect of the present invention can be applied to the gene therapy of patients having hereditary or acquired abnormality in apoptosis mediated by Fas ligand or Fas antigen. That is, therapeutic and preventive treatments of patients suffering from articular rheumatism, SLE and the like autoimmune diseases and AIDS, hepatitis, nephritis and the like diseases can be carried out by connecting the novel DNA fragment of the present invention to an appropriate vector and introducing it directly into the living body or cells.

Detailed Description Text (102):
Purification of the novel Fas antigen derivative of the first aspect of the present invention from the aforementioned culture mixture is carried out by optionally selecting appropriate means from those which are generally used in the purification of polypeptides. Illustratively, the purification may be carried out by optionally combining appropriate means selected from usually used techniques such as salting-out, ultrafiltration, isoelectric precipitation, gel filtration, electrophoresis, ion exchange chromatography, hydrophobic chromatography, antibody chromatography and the like various affinity chromatographic techniques, chromatofocasing, adsorption chromatography, reverse phase chromatography and the like, if necessary further using a HPLC system and the like. Particularly, an affinity chromatography which uses an anti-Fas antibody capable of recognizing the novel Fas antigen derivative of the present invention, a Fas ligand, protein A or the like as the ligand is also useful for the purification of said novel polypeptide.

Detailed Description Text (138):
Ammonium sulfate (mfd. by Wako Pure Chemical Industries) was added to, and dissolved in, one liter of COS-1/pM1304 culture supernatant to 70% saturation, and the solution was allowed to stand overnight at 4.degree. C. The thus formed precipitate was recovered by 30 minutes of centrifugation at 8,000 rpm and at 4.degree. C., suspended in phosphate-buffered saline (PBS) and then dialyzed against PBS. A 57 ml portion of the thus prepared suspension was diluted with two volumes of Affi-prep Protein A Binding Buffer (manufactured by Bio-Rad). After removing the insoluble matter by filtration, the resulting solution was applied to an Affi-prep Protein A Preparative Cartridge (7.3 ml, manufactured by Bio-Rad) column which has been equilibrated in accordance with the instructions. The column was washed with 90 ml of Affi-prep Protein A Binding Buffer and then shFas(nd29)-Fc was eluted with Affi-prep Protein A Elution Buffer (manufactured by Bio-Rad). Fractions containing shFas(nd29)-Fc which was detected by ELISA making use of a monoclonal antibody specific for human Fas antigen were pooled, subjected to ultrafiltration using Filtron Omega Cell (manufactured by Fuji Filter; nominal molecular weight cutoff of 30 kD) and then concentrated. The thus concentrated solution was dialyzed against 0.9% NaCl, thereby obtaining purified shFas(nd29)-Fc. Also, hFas-Fc was purified in the same manner. The protein content of each sample was measured in accordance with the method of Lowry using bovine serum albumin as the standard substance.

Detailed Description Text (153):
(1) Preparation of Anti-Fas Antigen Monoclonal Antibody-immobilized Affinity Column

Detailed Description Text (154):
A 350 mg portion of an anti-Fas antigen monoclonal antibody (4B4-B3) which has been prepared in accordance with a known method (Kohler and Milstein, Nature, vol. 256, p. 495, 1975) using mouse myeloma cells and spleen cells of mouse immunized with human Fas antigen was mixed with 120 ml of Formyl-Cellulofine (manufactured by Seikagaku Kogyo) and stirred at 4.degree. C. for 2 hours. This was then mixed with 650 mg of trimethylamine borane (manufactured by Wako Pure Chemical Industries) and stirred overnight to effect binding of the antibody. In order to remove un-immobilized antibody molecules, the resin was washed with 2.4 liters of ultra-pure water. Thereafter, this was stirred at 4.degree. C. for 3 hours in 0.2 M Tris-HCl (pH 8.0) together with 650 mg of trimetylamine borane to block unreacted formyl group, thereby obtaining the antibody affinity column.

Detailed Description Text (156):
A ten liter portion of COS-1/pM1317 culture supernatant was concentrated to 1.5 liters by ultrafiltration using Filtron Mini Set (manufactured by Fuji filter; 10 kD in nominal molecular weight cutoff). Thereafter, the concentrate was adjusted to pH 8.0 by adding 1 M Tris-HCl (pH 9.0) and applied to the anti-Fas antigen monoclonal antibody-immobilized affinity column which has been equilibrated in advance with 50 mM Tris-HCl 320ml of (pH 8.0) containing 1 M NaCl. After washing the column with 50 mM Tris-HCl (pH 8.0) containing 1 M NaCl, shFas(nd29)-hinge was eluted with 0.1 M glycine-HCl (pH 2.5) containing 1 M NaCl. Fractions containing shFas(nd29)-hinge detected by ELISA were pooled, subjected to ultrafiltration using Filtron Omega Cell (manufactured by Fuji filter; 10 kD in nominal molecular weight cutoff) and then concentrated. By dialyzing the concentrate against 0.9% NaCl, purified shFas(nd29)-hinge was obtained.

Detailed Description Text (177):
Since the novel polypeptide (novel Fas antigen derivative) of the present invention can inhibit induction of apoptosis by competitively inhibiting binding of a Fas ligand with a Fas antigen, it can be used for the prevention and treatment of various diseases in which the participation of apoptosis mediated by the Fas antigen is indicated, by controlling the apoptosis mediated by the Fas antigen, particularly an apoptosis generated in the living body caused by an endogenous or exogenous Fas ligand. For example, in the case of certain autoimmune diseases, it will become possible to prevent destruction of organs by inhibiting rapid cell death caused by the attack of autoantigen reactive T cells, through the artificial inhibition of apoptosis making use of the novel Fas antigen derivative. Illustrative examples of such diseases include graft versus host disease (GVHD) and diabetes. It is known that not only infected cells but also un-infected cells are removed by immune reactions when infected with viruses. For example, it is considered that decrease in the immunological capacity at the latter stage of AIDS virus infection and reduction of liver functions by hepatitis, particularly fulminant hepatitis, are results of extreme reduction of tissue functions caused by the apoptosis of immunocytes or hepatocytes. In the case of such conditions, the novel Fas antigen derivative capable of inhibiting apoptosis can be used for the treatment of apoptosis-related infectious diseases caused by viruses, such as influenza, AIDS, hepatitis and the like, and complications thereof. In addition, since Fas antigen seems to be related to the cell death in various organs because of its broad distribution in organs, it may also be useful for the treatment of myocardiopathy in myocardial infarction and the like ischemic heart diseases, such as reperfusion injury, nephritis and multiple organ failure and for the preservation organs at the time of organ transplantation. Particularly, since the novel Fas antigen derivative of the present invention can strongly inhibit apoptosis with a low dosage, it will also be effective in the living body with a low dosage and with less side effects, so that it has high availability from the viewpoint of efficacy, safety and cost. The novel Fas antigen derivative of the present invention which comprises a sequence of human origin is particularly desirable in applying it to human.

Detailed Description Text (179):
Also, since it keeps at least a part of the antigenicity of Fas antigen, it can be